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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,991	11/03/2003	E. Itzhak Lerner	1662/61902	5352

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KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,991	LERNER ET AL.	
	Examiner	Art Unit	
	JENNIFER MYONG M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-10,18-38,40 and 41* is/are pending in the application.

4a) Of the above claim(s) *19-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-10,18,32-38,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on October 17, 2008 has been entered.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 7-10, 18, 32-38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Obata Nobuko et al. (JP 09-249562) in view of Patel et al. (U.S.Patent No. 6,569,463B1) of record and further in view of Hoogendoorn et al. (U.S.Patent No. 4,150,113) of record and Pellegrini et al. (U.S.Patent No. 6,455,557B1).

Obata Nobuko et al. teach a tizanidine hydrochloride preparation comprising citric acid so that the pH of the preparation is adjusted to $\leq$ 5.5, preferably into the range of 2.2-5.4. Obata Nobuko et al. teach that the preparation can be formulated into tablets, capsules, granules, powder, etc. Obata Nobuko et al. teach that the tizanidine

preparation is known as having a muscle relaxant property. Obata Nobuko et al. teach that additives such as a disintegrant can be formulated with the tizanidine preparation. (abstract).

Obata Nobuko et al. do not teach buccal or sublingual administration, the specified disintegrants (i.e. microcrystalline cellulose), percentages of bioavailability comparison set forth in claims 7 and 32-34, 37 and 38, the numeric anti-spasmodic amount of tizanidine set forth in claims 35-36, the immediate formulation of tizanidine being compared set forth in claims 8-10 and obtaining saliva with a pH of 2 to 7.

Patel et al. teach that tizanidine composition comprising various excipients can be administered by buccal/sublingual route. (column 28, column 31). Patel et al. teach that the solid buccal or sublingual composition provide a rapidly dissolvable and more solubilized state with improved absorption and/or bioavailability of tizanidine. (column 2, lines 15-40, claims 5-9,23,25, 34,35,37, 49 and 51). Patel et al. teach that microcrystalline cellulose is one of disintegrants or super disintegrants. (column 32, lines 10-15).

Hoogendoorn et al. teach that as far as pH is concerned, the pH of the saliva is normally about 7.0 to 7.5. Upon the consumption of certain types of foods, particularly, those containing sugar, generation of acid takes place, with lowering the pH down to 5.5 to 4.5. (column 1, lines 45-50).

Pellegrini et al. teach that Tizanidine is pharmacologically characterized as a central-acting alpha2 adrenoreceptor agonist which has myotonolytic activity useful in the treatment of spasticity in patients with muscle spasm and pain. Pellegrini et al.

teach that anti-spastic efficacy has been demonstrated for tizanidine in placebo-controlled trials, with reduction in mean muscle tone scores of 21 to 37% versus 4 to 9% for patients receiving placebo. (column 1 particularly lines 10-15, lines 40-45).

It would have been obvious to one of ordinary skill in the art to modify the route of administration of Obata Nobuko et al. to sublingual or buccal administration for the treatment of muscle spasms because tizanidine is well known having muscle relaxant effect and because Patel et al. teach that solid oral tizanidine composition comprising various excipients can be administered via buccal/sublingual route. Further, Patel et al. teach that the buccal or sublingual administration of a composition comprising tizanidine improves the absorption and/or bioavailability of tizanidine. One would have been motivated to make such modification in order to achieve improved absorption and/or bioavailability of tizanidine by rapidly dissolving buccal or sublingual route of administration. There is a reasonable expectation of successfully treating muscle spasm with buccal/sublingual administration of tizanidine formulation taught by Obata Nobuko et al. because Patel et al. teach that buccal/sublingual administration of tizanidine increases bioavailability and improves absorption of tizanidine. The percentages of the drug release and increasing bioavailability of the drug set forth in claims 7 and 32-34, 37 and 38 is obvious result upon the buccal/sublingual administration of the same active agent tizanidine comprising the same acidulant taught by Obata Nobuko et al. and a disintegrant would obviously increased bioavailability and absorption of tizanidine. There is a lack of teaching in the specification that the specified disintegrants in the applicants' tizanidine composition is critical.

With regard to the numeric value of the antispasmodic amount set forth in claims 35 and 36, such is obvious and encompassed by the teaching of Obata Nobuko because Obata Nobuko et al. teach that the tizanidine preparation is known as having a muscle relaxant property. One of ordinary skill in the art would have been motivated to determine its optimum numeric antispasmodic amount in order to provide proper optimum dosages required for the patients to be treated. With regard to the acidulant (i.e. citric acid) utilized by Obata Nobuko et al. to obtain saliva with a pH of 2 to 7, such is obvious because Hoogendoorn et al. teach that as far as pH is concerned, the pH of the saliva is normally about 7.0 to 7.5. Upon the consumption of certain types of foods, particularly, those containing sugar, generation of acid takes place, with lowering the pH down to 5.5 to 4.5. (column 1, lines 45-50). It is noted that the tizanidine preparation comprising citric acid taught by Obata Nobuko et al. provide pH of $\leq$ 5.5, preferably into the range of 2.2-5.4. Therefore, upon the administration of Obata Nobuko's acidic tizanidine preparation as modified by Patel et al., would provide saliva with pH less than the normal pH of saliva. With regard to the claimed disintegrant such as microcrystalline cellulose, such is obvious choice because Obata Nobuko teach that tizanidine preparation can be formulated with disintegrants and because the disintegrant such as microcrystalline cellulose is a super disintegrant and it is routinely formulated as a super disintegrant in tizanidine formulations taught by Patel et al. Therefore, disintegrants such as microcrystalline in tizanidine formulation is well known in the art at time the invention was made.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

Response to Arguments

Applicants' arguments filed October 17, 2008 have been fully considered but they are not persuasive. Applicants argue that JP'562 does not suggest a method of treating muscle spasms by administering a rapidly dissolving tablet which dissolves in the mouth; therefore, it fails to render the claims obvious. This is not found to be persuasive because Obata Nobuko et al. teach that the tizanidine preparation is known as having a muscle relaxant property. This teaching is further supported by Pellegrini et al. who teach the efficacy of tizanidine for the treatment of muscle spasm is well known in the art at time the invention was made. Applicants argue that the '463 patent focus on the delivery system (requiring encapsulation) and not on the active pharmaceutical ingredient; this is clear from the enumeration of a never-ending list of drugs, that is a list of active ingredient that is over five columns long. This is not found to be persuasive because Patel et al. teach that tizanidine composition comprising various excipients can be administered by buccal/sublingual route. Therefore, Patel et al. clearly named tizanidine and it can be formulated to administer by buccal/sublingual route. The Patel et al's comprehensiveness of the listing do not negate the fact that the claimed compound, tizanidine, was specifically taught for the specified route of

administration. Applicants argue that the '113 patent is directed to dentifrice containing an enzyme, which is a non-analogous subject matter to the method of treating muscle spasm. The reference states that a pH value of 5.5 to 4.5 is achieved during eating and that the zone below 5.5 is often called the danger zone because it leads to tooth decay. Therefore, this reference teaches against the pH range of the instant claims. This is not found to be persuasive because instant claims are drawn to an acidulant in an amount to obtain saliva with a pH of 2 to7 wherein the acidulant is citric acid. Obata Nobuko et al. teach a tizanidine hydrochloride preparation comprising citric acid so that the pH of the preparation is adjusted to $\leq$ 5.5, preferably into the range of 2.2-5.4. Therefore, the amount of citric acid utilized by Obata Nobuko et al. encompasses Applicants' claimed acidulant amounts required by the claims.

Applicants argue that the rejection is an example of the piece meal analysis and the rejection lack fundamental reasoning as to why the skilled artisan would combine such references and whether the skilled artisan would have a reasonable expectation of success. This is not found to be persuasive because applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

None of the claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
January 3, 2009